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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,660	GAYLE III ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 19-41* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 20-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05; 8/21/02;* 6/18/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 1-6 and 19-41 are pending.

2. Applicant's election with traverse of Group 1, claims 1-4, 20, 22, 24, 26, 28, 30, 32, 33, 35-36, 38 and 40 (now Claims 1-6 and 20-41) drawn to a method for inhibiting platelet activation and recruitment in a mammal by administering a soluble CD39 polypeptide having X-Y wherein X is Ala or mature IL-2 capable of adopting a stable secondary structure and Y is a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 2, fragment or variant thereof, filed 8/26/05, is acknowledged. The traversal is on the grounds that Claim 34 has been amended to directly depend from Claim 1. Claims 33 and 35 depend indirectly on Claim 5 which is the basis for the other 8 groups. Claim 35 has been amended to depend directly on Claim 5. Accordingly, Group 1 should include Claims 1-4, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40. Second, the examiner break unity of invention citing Gayle et al. publication (J. Clin. Invest 1 0 1 (9): 1 85 1 - 1 859, May 1 998) which is applicant's own work. If the Examiner is asserting a § 1 02 or § 103 rejection of the claims over Gayle et al, Applicants believe they will be able to overcome the rejection because Gayle et al. Third, the Examiner appears to be arguing that since Applicants' claimed invention does not contribute a special technical feature over the prior art, they do not have a single general inventive concept and lack unity of invention. Applicants respectfully submit that the Examiner is misapplying the unity of invention standard by applying the reference to each of Applicants' claims. Any prior art should be applied to the independent claims in order to determine whether the corresponding dependent claims still contain an inventive link. Accordingly, Gayle et al. cannot be the basis for a valid restriction requirement. Under the proper standard, the claims of the present application all share a single inventive concept as they are all directed to methods for using novel and non-obvious fusion polypeptides. Each of the claim groups defines a method for using a fusion polypeptide that contains at its C-terminal portion soluble CD39. Accordingly, the special technical feature of each claim group is the use of a fusion protein containing at its C-terminal portion soluble in methods for inhibiting platelet activation and recruitment in a mammal (Claims 1-7 and 20-41) or for degrading nucleoside tri- and/or di- phosphates (Claim 1 9), which is thought to be the mechanism that inhibits platelet activation. The claim groups only differ with respect to the N-terminal portion of the fusion polypeptide that is used in the claimed method. The various N-terminal portions used in the

claim groups all have the same function of promoting the extracelluar secretion of the polypeptide. Accordingly, the use of these particular fusion polypeptides is the single general inventive concept that links the claim groups together. Moreover, the Examiner who completed the PCT Written Opinion did not find lack of unity in the claims even though claims 1 -20 as originally filed contained the same types of inventions. See PCT Written Opinion dated August 1 8, 2000. The claims as now amended retain the same technical relationship as the original claims.

In response, the inventions listed as Groups 1-9 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The WO 96/30532 publication teaches a method of inhibiting platelet activation such as platelet aggregation for treating thrombotic disorders such as thrombosis, stroke, restenosis in a mammalian subject by administering an effective amount of soluble human CD39 protein (see claims 34-36, 39-40, page 11, page 2, reference SEQ ID NO: 1, in particular). The WO 96/30532 publication teaches variants of human CD39 such as derivatized or mutated or truncated human CD39 (see page 19, in particular). The WO 96/30532 publication teaches the reference method wherein the reference soluble CD39 polypeptide is administered in a composition comprising a pharmaceutically acceptable carrier (see page 28, fourth and fifth paragraphs, page 29, in particular). The reference pharmaceutical composition is administered in the form of a solution, suspension, tablets, pills, capsules, sustained release formulation or powders (see page 28, last paragraph, in particular). The reference soluble CD39 is administered in conjunction with anastomosis of vascular graft (see page 3, last paragraph, in particular).

The invention differs from the teachings of the reference only in that the method wherein the soluble polypeptide having a structure of X-Y wherein X is a heterologous peptide capable of adopting a stable secondary structure and Y is a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 2 or fragment of SEQ ID NO: 2 wherein said fragment have apyrase activity or variants of SEQ ID NO: 2 wherein said variants have apyrase activity.

Malizewski et al teach various soluble CD39 polypeptide having a structure of X-Y wherein the X is a heterologous peptide such as human IgG1 Fc domain linked to a soluble human or mouse CD39 polypeptide (see Figure 9 legend, page 3581, col. 2, second full paragraph, in particular). The reference heterologous peptide obviously capable of adopting a stable secondary structure. Malizewski et al teach various soluble polypeptide comprising human CD39-Fc and murine CD39-Fc (see Figure 9, in particular). The reference full length human

soluble CD39 is 100% identical to the full length polypeptide of claimed SEQ ID NO: 2 (see Figure 7, amino acid sequence of human CD39, in particular) which is at least 70%, 80%, 90%, 95%, 98% and 99% identical to the amino acid sequence to claimed amino acids 36 to 478 of SEQ ID NO: 2. The term "comprising" or "having" is open-ended. It expands the claimed 21-463 of SEQ ID NO: 3 to include additional amino acids at either or both ends to include the reference fusion or soluble human CD39 polypeptide. The reference soluble CD39 polypeptide is also a fusion polypeptide since the C terminal hydrophobic region of the human CD39 polypeptide is replaced with the human IgG1 Fc domain (see page 3581, col. 2, par. 2, in particular). Malizewski et al also teach variants of human CD39 such as murine CD39 (see figure 7, in particular). The reference human or murine soluble CD39 polypeptide is produced by culturing a recombinant host cell such as COS cell transfected with the cDNA encoding the full-length human or murine CD39-Fc (see Figure 8 legend, page 3575, col. 1, cDNA expression and immunoselection, in particular). Malizewski et al further teaches a composition comprising a pharmaceutically acceptable carrier such as PBS and the reference polypeptide (see page 3575, col. 2, Immunoprecipitation and SDS-PAGE, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit platelet activation using soluble CD39 polypeptide as taught by WO96/30532 or the soluble human CD39-Fc and murine CD39-Fc as taught by Malizewski et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/30532 publication teaches soluble CD39 polypeptide is useful for inhibiting platelet aggregation and for treatment of thrombotic disorders such as thrombosis, stroke, restenosis in a mammalian subject such as human (see claims 34-36, 39-40, page 11, page 2, in particular). Claims 32 and 34 are included in this rejection because it is within the purview of one of ordinary skilled in the pharmaceutical art to administer the reference soluble polypeptide parenterally or intravenously as taught by the WO 96/30532 publication (see page 28, last paragraph, in particular).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention.

Upon reconsideration, Group 2 has been rejoined with Group 1 to include the method of for inhibiting platelet activation and recruitment by administering fusion polypeptide comprising

SEQ ID NO: 6. SEQ ID NO: 6 is a fusion protein comprising the 12 amino acids from the N-terminus of IL2 fused to soluble CD39. Therefore, the requirement of Group 1 (now claims 1-6, and 20-41) and Groups 3-9 is still deemed proper and is therefore made FINAL.

3. Claim 19 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-6, and 20-41, drawn to a method for inhibiting platelet activation and recruitment in a mammal by administering a soluble CD39 polypeptide having X-Y wherein X is Ala or mature IL-2 capable of adopting a stable secondary structure and Y is a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 2, or SEQ ID NO: 6, are being acted upon in this Office Action.

5. Claims 3, 5 and 6 are objected to as the claims encompass non-elected embodiments.

6. Claims 20-21 are objected to because "A method" should have been "The method" for said dependent claims.

7. Claims 1 and 2 are objected to because the plural "polypeptides" in claim 1a, and claim 2(a)-(g) do not correlate with the singular soluble CD39 polypeptide recited in claim 1 at line 3.

8. Claim 5 is objected to because the plural "fusion polypeptides" in claim 5(b) does not match the singular "soluble CD39 polypeptide in claim 5, line 1.

9. The drawings, filed 4/16/01, are not approved because the background of Figure 4 is too dark.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6, and 20-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of inhibiting ADP-induced platelet

aggregation, activation and recruitment in vitro comprising administering an effective amount of a soluble human CD39 polypeptide comprising SEQ ID NO: 6 having apyrase, **does not** reasonably provide enablement for:

(1) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(2) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) polypeptides having a sequence consisting of amino acids 38-476 or 39-476 of SEQ ID NO:2; (b) any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to amino acids 36 to 478 of SEQ ID NO:2 or at least 70%, 80%, 90%, 95%, 98%, or 99% identical to any "fragment thereof", wherein said variant polypeptides have apyrase activity;

(3) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is any peptide fragment from the amino terminus portion of any mature IL-2 and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected

from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(4) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of A-B-Y wherein A is any 0-20 amino acids from the amino terminal portion of any IL-2, B is a linker of 0-15 amino acids, and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(5) a method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity;

(6) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell that encodes the soluble CD39 polypeptide under conditions permitting expression of the CD39 polypeptide and recovering the expressed CD39 polypeptide;

(7) a method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant "host cell that encodes" the soluble CD39 polypeptide under conditions permitting expression of the CD39 polypeptide and recovering the expressed CD39 polypeptide;

(8) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell comprises any DNA sequence which, due to degeneracy of the genetic code, encode the polypeptide encoded by SEQ ID NO: 5 or SEQID NO: 7;

(9) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell comprises any DNA sequence which, due to degeneracy of the genetic code, encode the polypeptide encoded by SEQ ID NO: 5 or SEQ ID NO: 7;

(10) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl

terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide is administered in a composition comprising a pharmaceutical carrier;

(11) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide is administered in combination with at least one other antithrombotic or antiplatelet composition or in combination with aspirin;

(12) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide is administered in a composition comprising a pharmaceutical carrier;

(13) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide is administered in combination with at least one other antithrombotic or antiplatelet composition, or in combination with aspirin;

(14) the a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble

polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble polypeptide is administered parentally or intravenously;

(15) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble polypeptide is administered parentally or intravenously;

(16) The methods mentioned above wherein the mammal is suffering from any disease such as the ones recited in claims 36-37;

(17) The methods mentioned above wherein the soluble CD39 is administered to "prevent" thrombus formation, or reformation, occlusion, reocclussion, stenosis, or restenosis of blood vessels, or stroke, and

(18) The method mentioned above wherein the soluble CD39 is administered in conjunction with angioplasty, carotid endarterectomy, anastomosis of vascular graft, atherectomy, stent placement, placement of a chronic cardiovascular device such as an in-dwelling catheter or prosthetic valve or vessel, or bypass surgery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of inhibiting platelet activation and recruitment comprising administering a soluble human CD39 comprising the SEQ ID NO: 6. The soluble human CD39 fusion polypeptide comprises a leader containing sequence consisting of the amino acid sequence of a human IL-2 polypeptide of SEQ ID NO: 9 fused to a soluble human CD39 polypeptide of SEQ ID NO: 2 that contains amino terminus 36-44 and the carboxyl terminus 471-478 of SEQ ID NO: 2. The specification further discloses a soluble human CD39 fusion protein comprising the amino acid sequence encoded by SEQ ID NO: 7 wherein the fusion protein contains a leader containing human IL2 leader, the first 12 amino acids of mature human IL2, fused to a peptide linker and soluble human CD39 (see page 37, lines 1-5). The soluble human CD39 polypeptide has been produced by culturing a recombinant host cell comprising a polynucleotide having a sequence selected from the group consisting of SEQ ID NO: 5 and SEQ ID NO: 7. The specification on page 9 discloses that CD39 polypeptides comprise one to ten deletions, insertions, or substitutions of amino acid residues, when compared to a native CD39 sequence. Variants of CD39 include polypeptides that are naturally occurring such as allelic forms, spliced forms, as well as that have been modifying in the amino acid sequence of a CD39 polypeptide or polynucleotide such as polypeptides are at least about 70%, 80%, 90%, 95%, 98% and 99% identical to the native CD39 of SEQ ID NO: 2 (page 10).

However, the specification does not teach how to make any and all CD39 polypeptide mentioned above for a method of inhibiting platelet activation, let alone "preventing" thrombus formations, reformation, occlusion, reocclusion, stenosis, restenosis, or stroke in any mammal suffering from a host of disease such as the ones recited in claims 36-37. This is because there is insufficient guidance as to the structure of any (1) "heterologous peptides capable of adopting a stable secondary structure" in the soluble CD39 polypeptide without the amino acid sequence (claim 1). Further, there is insufficient guidance as to the structure of any "fragments" of the polypeptides having an amino acid sequence set forth in SEQ ID NO: 2 having apyrase activity, or any "variants" of SEQ ID NO: 2 or any variant of fragment of SEQ ID NO: 2 having apyrase activity without the amino acid sequence. There is insufficient guidance as to which amino acids within the full length sequence of SEQ ID NO: 2 to be deleted, added, substituted or combination thereof such that the undisclosed fragment and variant maintain it structure and function. The term "having" is open-ended. It expands the soluble CD39 such as polypeptide as set forth in

claim 1(a), and any "fragments" thereof as set forth in claim 1(b) to include additional amino acids at either or both ends. There is in a lack of guidance as to which amino acids to be added, let alone the undisclosed soluble CD 39 polypeptide could prevent any diseases. There is also a lack of guidance as to which amino acids within which "fragments" of SEQ ID NO: 2 to be deleted, added or modified such that the resulting soluble CD39 polypeptide fragment and variants thereof maintains its structure and apyrase activity.

With regard to claim 2, the term "having" is open ended. It expands the amino acids 38-476 or 39-476 of SEQ ID NO: 2 to include additional amino acids; the specification does not teach which amino acids to be added. Further, the term "at least 70, 80, 90, 95, 98, 99 %" identical in amino acid sequence to 36 to 478 of SEQ ID NO: 2 means there is at least 30%, 20%, 10, 5, 3, 2 and 1 % difference, respectively, relative to 36 to 478 of SEQ ID NO: 2. This is equivalent to at least 131, 88, 44, 22, 9 and 4 amino acids difference, respectively. There is a lack of guidance as to which 131, 88, 44, 22, 9 or 4 amino acids relative to 36 to 478 of SEQ ID NO: 2 to be modified such as addition, deletion, substitution such that the resulting polypeptide maintains its structure and function. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program mentioned above, it is unpredictable which amino acid sequences will have 70% identity to the claimed sequences and still retain the activities. Thus it would require undue experimentation for one of skill in the art to identify amino acid sequences that not only are 70% identical to the claimed sequences but also have functional activity. Further, there is insufficient guidance as to the length of the "fragment thereof" without the amino acid sequence and because the size of the fragment is unknown in claim 2, it is unclear how one skilled in the art to go about finding the variant polypeptide having at least 70%, 80%, 90%, 95%, 98%, or 99% to the fragment and yet the polypeptides have apyrase activity.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction,

1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Grinthal et al teach that a single His to Gly substitution at position 59 in CD39 changes substrate specificity such as an apyrase to an adenosine diphosphatase (ADPase) in a manner that depends on intact associations of both transmembrane domains with the membrane (see abstract, in particular). Given the unlimited number of CD39 polypeptide, fragments, and variants thereof, there is insufficient in vivo working example the claimed method could inhibit platelet activity, let alone for treating or preventing any disease.

With regard to claim 3, there is insufficient guidance as to the structure of the "amino terminal portion of IL-2" in the peptide fragment X without the amino acid sequence. The "portion" could be as little as one amino acid or could be as long as 50 amino acids. In addition, the specification discloses only human IL-2, the specification does not teach any other IL-2 leader peptide.

With regard to claim 4, the same reasons stated above apply to claim 4 in terms of "fragments" and "variants". Further, there is insufficient guidance as to the structure and function of "A" such as which 0-20 amino acids from the terminal portion of mature IL-2 is part of the polypeptide in the claimed method. Likewise, there is insufficient guidance as to the structure and function of "B" such as which linker peptide of 0-15 amino acids is part of the polypeptide in the claimed method, let alone multiple "fragments" and "variants" of CD39. In particular, the

specification does not teach the *combination* of 0-20 amino acids from the amino terminal portion of any mature IL-2 and B is any linker of 0-15 amino acids and Y is any fragments, and any variants of SEQ ID NO: 2 for the claimed method.

With regard to claim 5, the specification does not teach any soluble CD39 polypeptide comprising "fusion polypeptides" comprising multiple polypeptides of SEQ ID NO: 6 or any combination thereof as set forth in claim 5(b). The specification merely discloses a fusion polypeptide comprising SEQ ID NO: 6 wherein the fusion polypeptide comprises human IL-2 leader fused to a peptide linker fused to a soluble human CD39 from amino acids 38-476 or 39-476 of SEQ ID NO: 2.

With regard to claims 20 and 21, the recombinant cell does not "encode" the soluble CD39 polypeptide. Rather, it is the nucleic acid that encodes the soluble CD39 polypeptide.

With regard to claims 36-37, given the unlimited number of soluble CD39 polypeptide, there is insufficient in vivo working examples showing the claimed method could treat any mammal suffering from any disease such as the one s recited in claim 36-37, much less the claimed method could "prevent" stroke or thrombus formation, or reformation, occlusion, reocclusion, stenosis, ore restenosis of blood vessels as set forth in claims 38-39. Given the unlimited number of CD39 polypeptide, fragments, variants thereof, it is unpredictable which polypeptide having the structure of X-Y or A-B-Y has apyrase activity, much less for treating any disease. Since the structure of the polypeptides mentioned above are not enabled, it follows that the claimed method of inhibiting platelet activation using the polypeptide made by the process of culturing recombinant host cell is not enabled. It also follows that methods of inhibiting platelet activation using any undisclosed polypeptide mentioned above in combination with any at least one other antithrombotic or antiplatelet composition or in conjunction with angioplasty, carotid endarterectomy, anastomosis of vascular graft, atherectomy, stent placement, placement of a chronic cardiovascular device such as an in-dwelling catheter or prosthetic valve or vessel, or bypass surgery are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

12. Claims 1-6, and 20-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(2) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) polypeptides having a sequence consisting of amino acids 38-476 or 39-476 of SEQ ID NO:2; (b) any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to amino acids 36 to 478 of SEQ ID NO:2 or at least 70%, 80%, 90%, 95%, 98%, or 99% identical to any "fragment thereof", wherein said variant polypeptides have apyrase activity;

(3) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is any peptide fragment from the amino

terminus portion of any mature IL-2 and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(4) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of A-B-Y wherein A is any 0-20 amino acids from the amino terminal portion of any IL-2, B is a linker of 0-15 amino acids, and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity;

(5) a method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity;

(6) a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino

terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell that encodes the soluble CD39 polypeptide under conditions permitting expression of the CD39 polypeptide and recovering the expressed CD39 polypeptide;

(7) a method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant "host cell that encodes" the soluble CD39 polypeptide under conditions permitting expression of the CD39 polypeptide and recovering the expressed CD39 polypeptide;

(8) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell comprises any DNA sequence which, due to degeneracy of the genetic code, encode the polypeptide encoded by SEQ ID NO: 5 or SEQID NO: 7;

(9) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide has been produced by culturing a recombinant host cell comprises any DNA sequence which, due to degeneracy of the genetic code, encode the polypeptide encoded by SEQ ID NO: 5 or SEQ ID NO: 7;

(10) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide is administered in a composition comprising a pharmaceutical carrier;

(11) the method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble CD39 polypeptide is administered in combination with at least one other antithrombotic or antiplatelet composition or in combination with aspirin;

(12) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide is administered in a composition comprising a pharmaceutical carrier;

(13) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble CD39 polypeptide is administered in combination with at least one other antithrombotic or antiplatelet composition, or in combination with aspirin;

(14) the a method for inhibiting platelet activation and recruitment in any mammalian subject in need of such treatment comprising administering an effective amount of any soluble polypeptide having a structure of X-Y wherein X is Ala residue or any heterologous peptides capable of adopting a stable secondary structure and Y is selected from the group consisting of (a) any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478, (b) any "fragments" of any polypeptide "having" an amino acid sequence as set forth in SEQ ID NO: 2 wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting amino acids 471-478 wherein said have apyrase activity, and (c) any variants of any (a) or (b) mentioned above wherein said variants have apyrase activity wherein the soluble polypeptide is administered parentally or intravenously;

(15) the method of inhibiting platelet activation and recruitment in any mammal in need of such treatment comprising administering an effective amount of any "fusion polypeptides" comprising the polypeptide of SEQ ID NO: 6 wherein said fusion polypeptides have apyrase activity wherein the soluble polypeptide is administered parentally or intravenously;

(16) The methods mentioned above wherein the mammal is suffering from any disease such as the ones recited in claims 36-37;

(17) The methods mentioned above wherein the soluble CD39 is administered to "prevent" thrombus formation, or reformation, occlusion, reocclussion, stenosis, or restenosis of blood vessels, or stroke, and

(18) The method mentioned above wherein the soluble CD39 is administered in conjunction with angioplasty, carotid endarterectomy, anastomosis of vascular graft, atherectomy, stent placement, placement of a chronic cardiovascular device such as an in-dwelling catheter or prosthetic valve or vessel, or bypass surgery.

With the exception of the specific soluble human CD39 fusion protein comprising SEQ ID NO: 6 encoded by SEQ ID NO: 5 or 7 mentioned above for the claimed method of inhibiting

platelet activation, there is insufficient written description about the structure associated with function of any and all soluble CD39 polypeptide without the amino acid sequence for the claimed method. There is inadequate written description about the structure of the "heterologous peptide capable of adopting a stable secondary structure" in claim 1 without the amino acid sequence. In addition, the term "having" is open-ended. It expands the soluble CD39 such as polypeptide as set forth in claim 1(a) to include additional amino acids at either or both ends. There is a lack of written description about which amino acids within the full length CD39 polypeptide to be added such that the resulting soluble CD39 polypeptide and variants thereof maintains its structure and biological activity.

With regard to "fragments", the term "having" is open-ended. There is a lack of written description about which amino acids in the "fragments" of claims 1(b) or "fragments" of 36 to 478 of SEQ ID NO: 2 to be added such that the resulting soluble CD39 polypeptide fragments and variants thereof maintain its structure and apyrase activity.

With regard to "variants", the term "at least 70, 80, 90, 95, 98, 99 %" identical in amino acid sequence to a fragment of amino acids 36 to 478 of SEQ ID NO: 2 is ambiguous because the size of the fragment is unknown in claim 2. Even if the soluble CD39 polypeptide is limited to amino acids 36 to 478 of SEQ ID NO: 2, a polypeptide having a sequence "at least 70%, 80%, 90%, 95%, 98% and 99% identical to 36 to 478 of SEQ ID NO: 2 means 30%, 20%, 10%, 5%, 2% and 1% differences, respectively. The soluble CD39 polypeptide in the claimed method is equivalent to having at least 133, 88, 44, 22, 8 and 4 amino acids difference relative to 36 to 478 of SEQ ID NO: 2. There is insufficient disclosure as to which 131, 88, 44, 22, 9 and 4 amino acids relative to 36 to 478 of SEQ ID NO: 2 to be modified such as addition, deletion, substitution such that the resulting polypeptide maintains its structure and function.

With regard to claim 4, the same reasons stated above apply to claim 4 in terms of "fragments" and "variants". Further, there is inadequate disclosure about the structure and function of "A" such as which 0-20 amino acids from the terminal portion of mature IL-2 are part of the fusion polypeptide. Likewise, there is inadequate disclosure about the structure and function of "B" such as which linker peptide of 0-15 amino acids and Y such as soluble CD39 polypeptide are part of the fusion protein without the amino acid sequence, let alone the fusion protein comprising A-B-Y wherein the Y is any multiple "fragments" and "variants" of any CD39. In particular, the specification does not teach the *combination* of 0-20 amino acids from the amino terminal portion of any mature IL-2 and B is any linker of 0-15 amino acids and Y is

any fragments, and any variants of SEQ ID NO: 2 for the claimed method. The specification does not describe a method of inhibiting platelet activation comprising administering a polypeptide having the structure of A-B-Y wherein A is 0 amino acids from the amino terminal portion of any mature IL-2, B is a linker of 0 amino acids and Y is any fragments or variants of SEQ ID NO: 2. Likewise, the specification does not describe a method of inhibiting platelet activation comprising administering a polypeptide having the structure of A-B-Y wherein A is 0 amino acids from the amino terminal portion of any mature IL-2, B is a linker of 1 amino acid and Y is any fragments or variants of SEQ ID NO: 2.

With regard to claim 5, the specification does not describe any soluble CD39 polypeptide comprising "fusion polypeptides" comprising multiple polypeptides of SEQ ID NO: 6 or any combination thereof as set forth in claim 5(b). The specification merely discloses a fusion polypeptide comprising SEQ ID NO: 6 wherein the fusion polypeptide comprises human IL-2 leader fused to a peptide linker fused to a soluble human CD39 from amino acids 38-476 or 39-476 of SEQ ID NO: 2.

With regard to claims 20 and 21, the recombinant cell does not "encode" the soluble CD39 polypeptide. Rather, it is the nucleic acid that encodes the soluble CD39 polypeptide.

Given the unlimited number of soluble CD39 polypeptide, fragments, variants thereof and without the amino acid sequence, the polypeptide having the structure of X-Y or A-B-Y has apyrase activity without the amino acid sequence is not adequately described. Since the structure of the soluble CD39 polypeptide is not adequately described, it follows that the claimed method of inhibiting platelet activation using the undisclosed polypeptide made by the process of culturing recombinant host cell is not adequately described. It also follows that methods of inhibiting platelet activation using any undisclosed polypeptide mentioned above in combination with any other antithrombotic or antiplatelet composition or in conjunction with angioplasty, carotid endarterectomy, anastomosis of vascular graft, atherectomy, stent placement, placement of a chronic cardiovascular device such as an in-dwelling catheter or prosthetic valve or vessel, or bypass surgery are not adequately described.

Finally, the specification discloses only human soluble CD39 polypeptide and a fusion polypeptide comprising SEQ ID NO: 6, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of CD39, variants and fragment thereof as well as fusion polypeptide to describe the genus of polypeptide for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli*

Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 1, and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "polypeptide having an amino acid sequence as set forth in (SEQ ID NO: 2) wherein the amino terminus *is selected from the group consisting of amino acids* 36-44 and the carboxyl terminus *is selected from the group consisting of* amino acids 471-478;" in claim 1(a) is ambiguous because the polypeptide as set forth in SEQ ID NO: 2 is already contains the amino terminus consisting of amino acids 36-44 and the carboxyl terminus consisting of amino acids 471-478. It is not clear what is meant by "wherein the amino terminus *is selected from the group consisting of amino acids* 36-44 and the carboxyl terminus *is selected from the group consisting of* amino acids 471-478;". One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "amino terminal portion of mature IL-2" in claim 3 is ambiguous and indefinite because the term "portion" could be as little as one amino acid or it could be as long as 50 amino acids. It is not clear which particular amino acids in the mature IL-2 are part of the peptide fragment. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-2, 20, 26, 32, 34, 36, 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30532 (Oct 3, 1996; PTO 1449) in view of Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449).

The WO 96/30532 publication teaches a method of inhibiting platelet activation such as platelet aggregation for treating thrombotic disorders such as thrombosis, stroke, restenosis in a mammalian subject by administering an effective amount of soluble human CD39 protein (see claims 34-36, 39-40, page 11, page 2, reference SEQ ID NO: 1, in particular). The WO 96/30532 publication teaches variants of human CD39 such as derivatized or mutated or truncated human CD39 (see page 19, in particular). The WO 96/30532 publication teaches the reference method wherein the reference soluble CD39 polypeptide is administered in a composition comprising a pharmaceutically acceptable carrier (see page 28, fourth and fifth paragraphs, page 29, in particular). The reference pharmaceutical composition is administered in the form of a solution, suspension, tablets, pills, capsules, sustained release formulation or powders (see page 28, last paragraph, in particular). The reference soluble CD39 is administered in conjunction with anastomosis of vascular graft (see page 3, last paragraph, in particular).

The invention differs from the teachings of the reference only in that the method wherein the soluble polypeptide having a structure of X-Y wherein X is a heterologous peptide capable of adopting a stable secondary structure and Y is a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 2 or fragment of SEQ ID NO: 2 wherein said fragment have apyrase activity or variants of SEQ ID NO: 2 wherein said variants have apyrase activity.

Malizewski et al teach various soluble CD39 polypeptide having a structure of X-Y wherein the X is a heterologous peptide such as human IgG1 Fc domain linked to a soluble human or mouse CD39 polypeptide (see Figure 9 legend, page 3581, col. 2, second full

paragraph, in particular). The reference heterologous peptide is obviously capable of adopting a stable secondary structure. Malizewski et al teach various soluble polypeptide comprising human CD39-Fc and murine CD39-Fc (see Figure 9, in particular). The reference full length human soluble CD39 is 100% identical to the full length polypeptide of claimed SEQ ID NO: 2 (see Figure 7, amino acid sequence of human CD39, in particular) which is at least 70%, 80%, 90%, 95%, 98% and 99% identical to the amino acid sequence to claimed amino acids 36 to 478 of SEQ ID NO: 2. The term "comprising" or "having" is open-ended. It expands the claimed 21-463 of SEQ ID NO: 3 to include additional amino acids at either or both ends to include the reference fusion or soluble human CD39 polypeptide. The reference soluble CD39 polypeptide is also a fusion polypeptide since the C terminal hydrophobic region of the human CD39 polypeptide is replaced with the human IgG1 Fc domain (see page 3581, col. 2, par. 2, in particular). Malizewski et al also teach variants of human CD39 such as murine CD39 (see figure 7, in particular). The reference human or murine soluble CD39 polypeptide is produced by culturing a recombinant host cell such as COS cell transfected with the cDNA encoding the full-length human or murine CD39-Fc (see Figure 8 legend, page 3575, col. 1, cDNA expression and immunoselection, in particular). Malizewski et al further teaches a composition comprising a pharmaceutically acceptable carrier such as PBS and the reference polypeptide (see page 3575, col. 2, Immunoprecipitation and SDS-PAGE, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit platelet activation using soluble CD39 polypeptide as taught by WO96/30532 or the soluble human CD39-Fc and murine CD39-Fc as taught by Malizewski et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/30532 publication teaches soluble CD39 polypeptide is useful for inhibiting platelet aggregation and for treatment of thrombotic disorders such as thrombosis, stroke, restenosis in a mammalian subject such as human (see claims 34-36, 39-40, page 11, page 2, in particular). Claims 32 and 34 are included in this rejection because it is within the purview of one of ordinary skilled in the pharmaceutical art to administer the reference soluble polypeptide parenterally or intravenously as taught by the WO 96/30532 publication (see page 28, last paragraph, in particular).

18. Claims 3-5, 21-25, 27, 29, 31, 33, 35, 37, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30532 (Oct 3, 1996; PTO 1449) in view of Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449) as applied to claims 1-2, 20, 26, 32, 34, 36, 38 and 40 and further in view of Cullen et al (DNA 7(9): 645-650, 1988; PTO 1449).

The combined teachings of WO 96/30532 publication and Malizewski et al have been discussed supra.

The claimed invention in claim 3 differs from the combined teachings of the references only in that the method wherein X is a peptide fragment from the amino terminal portion of mature IL-2.

The claimed invention in claim 4 differs from the teachings of the reference only in that the polypeptide having a structure A-B-Y wherein A is 5-10 amino acids from the amino terminal portion of mature IL-2, B is a linker of 1 amino acid and Y is soluble CD39 polypeptide.

Cullen et al teach leader peptide such as IL-2 amino terminal fragment of IL-2 of five to ten amino acids in length or rat preproinsulin II operably linked to the N-terminus of any polypeptide such as IL-2 via an amino acid linker (see abstract, Fig 1, page 648, col. 1, first full paragraph, in particular). The heterologous leader peptide significantly enhances the secretion of the desired polypeptide (see page 645, col. 2, first full paragraph, page 648, col. 1, first and second paragraph, Table 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the leader peptide in amino terminal portion of CD39 polypeptide as taught by Malizewski et al for the heterologous leader peptide such as leader peptide from the amino terminal portion of mature IL-2 as taught by Cullen et al that significantly enhance the secretion of the fusion protein. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because heterologous leader peptide significantly enhances the secretion of the desired polypeptide as taught by Cullen et al (see page 645, col. 2, first full paragraph). Claims 33 and 35 are included in this rejection because it is within the purview of one of ordinary skilled in the pharmaceutical art to administer the reference soluble polypeptide parenterally or intravenously as taught by the WO 96/30532 publication (see page 28, last paragraph, in particular). Although the references do not teach the claimed nucleic acid sequence of SEQ ID NO: 5 or 7, claims 22-25 are included in

this rejection because the reference nucleic acid obviously is a sequence due to degeneracy of the genetic code that encoded the claimed soluble CD39 comprising IL2 leader fused to human CD39.

19. Claims 1, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30532 (Oct 3, 1996; PTO 1449) in view of US Pat No. 5,741,771 (April 21, 1998; PTO 892).

The teachings of WO 96/30532 publication have been discussed supra.

The claimed invention in claim 28 differs from the combined teachings of the references only in that the method wherein soluble CD39 polypeptide is administered in combination with at least one other anti-thrombotic or anti-platelet composition.

The claimed invention in claim 30 differs from the combined teachings of the references only in that the method wherein soluble CD39 polypeptide is administered in combination with aspirin

The '771 patent teaches anti-thrombotic or antiplatelet composition comprising aspirin in combination with other agent such as BB-10153 which is a anti-thrombotic agent for a method of treating antithrombotic therapy (see entire document, claims of '771 patent, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the aspirin or anti-thrombotic agent as taught by the '771 patent with the composition comprising soluble human CD39 protein for treating thrombotic disorders such as thrombosis, stroke, restenosis as taught by the WO 96/30532 publication (see claims 34-36, 39-40, page 11, page 2, reference SEQ ID NO: 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

20. Claims 1, 3-6, 21-25, 27, 29, 33, 35, 37, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30532 (Oct 3, 1996; PTO 1449) in view of Gayle et al (J Clinical

Investigation 101(9): 1851-1859, May 1998; PTO 1449) as evidenced by Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449).

The teachings of WO 96/30532 publication have been discussed supra.

The claimed invention in claim 3 differs from the combined teachings of the references only in that the method wherein X is a peptide fragment from the amino terminal portion of mature IL-2.

The claimed invention in claim 4 differs from the teachings of the reference only in that the method wherein the polypeptide having a structure A-B-Y wherein A is 5-10 amino acids from the amino terminal portion of mature IL-2, B is a linker of 1 amino acid and Y is soluble CD39 polypeptide.

Gayle et al teach a method of inhibiting platelet activation by administering a polypeptide having a structure X-Y wherein X is a heterologous peptides capable of adopting a stable secondary structure such as the amino terminal or leader sequence of the mature IL-2 fused to Flag peptide of 10 amino acids and wherein Y is a soluble human CD39 comprising the human coding sequence from Thr 38 to Thr 476 identical to the claimed SEQ ID NO: 2 (see page 1852, col. 1, Expression plasmid construction, Figure 1, in particular) as evidence by Malizeqski et al (see page 3577 of J immunol, Figure 2 and Figure 7 of Malizeqski). The reference polypeptide comprising a soluble human CD39 (38-476) or the full length human CD39 inherently has apyrase activity (see Figure 1, solid domain, page 1851, col. 2, first full paragraph, in particular). Gayle et al further teach a polypeptide having the structure of A-B-Y wherein the reference A is the amino terminal portion of mature IL-2, B is a linker such as FLAG of 10 amino acids which is within the claimed linker of 0-15 amino acids and Y is soluble CD39 polypeptide having an amino acid sequence depicted in Figure 1 that has amino acids Thr38 to Thr 476 of SEQ ID NO: 2 (see page 1852, col. 1, Expression plasmid construction, Fig. 1, in particular) as evidence by Malizeqski et al (see page 3577, Figure 2 of Malizeqski). Claims 5-6 are included in this rejection because the term "comprising" or "has" is open-ended. It expands the soluble polypeptide Thr 38 to Thr 476 of SEQ ID NO: 2 to include additional amino acids residues at either or both ends to include the reference full-length CD39. The reference polypeptide is produced by a process of preparing a soluble CD39 polypeptide comprising culturing a recombinant cell such as COS cell or CHO cell under condition to permit expression of the reference CD39 polypeptide and recovering the reference polypeptide from the culture (see Methods on page 1852, col. 1, in particular). Gayle et al teach a composition comprising the

reference polypeptide such as soluble CD39 and a pharmaceutically acceptable carrier such as sodium phosphate or PBS or Hepes (see page 1852, col. 2, first full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the soluble CD39 polypeptide for a method of inhibiting platelet activation or treatment of thrombosis or strokes as taught by the WO96/30532 for the soluble human or mouse CD39 polypeptide comprising amino terminal or leader sequence of the mature IL-2 fused to Flag peptide of 10 amino acids and wherein Y is a soluble human CD39 comprising the human coding sequence from Thr 38 to Thr 476 identical to the claimed SEQ ID NO: 2 as taught by Gales et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/30532 publication teaches soluble CD39 polypeptide is useful for inhibiting platelet aggregation and for treatment of thrombotic disorders such as thrombosis, stroke, restenosis in a mammalian subject such as human (see claims 34-36, 39-40, page 11, page 2, in particular). Claims 33 and 35 are included in this rejection because it is within the purview of one of ordinary skilled in the pharmaceutical art to administer the reference soluble polypeptide parenterally or intravenously as taught by the WO 96/30532 publication (see page 28, last paragraph, in particular). Although the references do not teach the claimed nucleic acid sequence of SEQ ID NO: 5 or 7, claims 22-25 are included in this rejection because the reference nucleic acid obviously is a sequence due to degeneracy of the genetic code that encoded the claimed soluble CD39 comprising IL2 leader fused to human CD39.

21. Claims 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30532 (Oct 3, 1996; PTO 1449) in view of Gayle et al (J Clinical Investigation 101(9): 1851-1859, May 1998; PTO 1449) as evidenced by Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449) as applied to claims 1, 3-6, 21-25, 27, 29, 33, 35, 37, 39 and 41 mentioned above and further in view of US Pat No. 5,741,771 (April 21, 1998; PTO 892).

The combined teachings of WO 96/30532 publication, Gayle and Malizeqski et al have been discussed supra.

The claimed invention in claim 29 differs from the combined teachings of the references only in that the method wherein soluble CD39 polypeptide is administered in combination with at least one other anti-thrombotic or anti-platelet composition.

The claimed invention in claim 31 differs from the combined teachings of the references only in that the method wherein soluble CD39 polypeptide is administered in combination with aspirin

The '771 patent teaches anti-thrombotic or anti-platelet composition comprising aspirin in combination with other agent such as BB-10153 which is a anti-thrombotic agent for a method of treating anti-thrombotic therapy (see entire document, claims of '771 patent, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the aspirin or anti-thrombotic agent as taught by the '771 patent with the composition comprising soluble human CD39 protein fusion protein for treating thrombotic disorders such as thrombosis, stroke, restenosis as taught by the WO 96/30532 publication and Gayle and Malizeqski et al (see claims 34-36, 39-40, page 11, page 2, reference SEQ ID NO: 1, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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